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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,897	10/22/2003	Mahavir Singh Khanna	RLL-297US	6343

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EXAMINER	
MORRIS, PATRICIA L	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,897	KHANNA ET AL.	
	Examiner	Art Unit	
	Patricia L. Morris	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6,7,9,10,12,14 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,7,9,10,12,14 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 4, 6, 7, 9, 10, 12, 14 and 39-41 are under consideration in this application.

Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2007 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 6, 7, 9, 10, 12, 14 and 39-41 are rejected under 35 U.S.C. 102(a) and/or (e) as being anticipated by Sherman, Vijayaraghavan et al., Kamiyama et al. and Gustavsson et al. for the reasons set forth in the previous Office action.

Again, Sherman et al. and Vijayaraghavan et al. al. specifically disclose the instant amorphous racemate salts of omeprazole. Note example 3 of Sherman et al. or example 1 of

Vijayarghan et al. Kamiyama et al. specifically disclose the amorphous form of the R-enantiomer in examples 4 and 5 therein. Gustavsson et al. specifically includes amorphous forms of the sodium salt of the racemate. Note column 2, lines 28-32, therein. Hence, the instant compound is deemed anticipated therefrom. Further, the pharmaceutical compositions are deemed anticipated therefrom. On page 6 of the specification, the instantly claimed compositions are dislosed to be made from conventional processing into tabletes, capsules, pills or solutions. Factual evidence from the prior art shows that all compounds dissolved in liquids become amorphous. (see Ulicky, page 21).

Applicants assert that the references fail the instant amorphous esomeprazole magnesium of certain chiral purity. As set forth below, applicants have now added new matter and there is no support for newly recited chiral purities. Assuming arguendo that applicants have support for the newly added chiral purities, applicants have failed to present any objective evidence showing that the instant amorphous form or the amorphous form in the pharmaceutical compounds is any different from the prior art amorphous forms.

Further, applicants allege that Sherman fails to recite X-ray diffraction data. However, it is well known in the art that all X-ray diffraction pattern of amorphous forms consists of a single broad, shallow peak termed an *amorphous halo*. Note page 578 of Nerurkar. Any X-ray diffraction of an amorphous material is only to show no diffraction or non-crystalline. One of having ordinary skill in the art would know that X-ray diffraction data alone does not define a product. Powdered X-ray diffraction is extremely unpredictable as evidenced by Bernstein; completely different X-ray pattern can be observed for the same crystal (p. 118) and same X-ray pattern can be found in completely different material (p. 272).

Claim Rejections - 35 USC ∋ 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Sherman, Vijayaraghavan et al., Kamiyama et al. and Gustavsson et al. in view of Bohlin et al. and Broeckx et al. for the reasons set forth in the previous Office action.

Again, the references disclose the instant amorphous racemic and R-isomeric salts as well as the pharmaceutical compositions. Further, Bohlin et al. disclose that it is well known in the art that S-omeprazole exists in amorphous, partly crystalline or substantially crystalline forms. Note column 1, lines 58-60, therein. Bohlin et al. and Broeckx et al. teach that omperazole is a racemic mixture that consists of two single enantiomers. Hence, the claimed

isomer as well as its relative selectivity of properties *vis-à-vis* the racemate are suggested by the references.

Contra to applicants' arguments in the instant response, Sherman and Vijayaraghavan et al. specifically disclose the amorphous racemic salts of omeprazole. The racemate consists of the R- and S-isomers as taught by Bohlin et al. and Broeckx et al. Accordingly, in the instant case, since the formula has a stereogenic sulfur, one merely has to select two possible enantiomers, R- and S-enantiomers. In this case, the **amorphous** S-enantiomer.

Mere arguments from counsel do not take the place any objective evidence. Applicants have failed to show any advantage for the instant amorphous salts and compositions. An X-ray diffraction of an amorphous material is only to show no diffraction or the non-crystalline nature of the material. X-ray diffraction pattern of an amorphous form consists of a single broad, shallow peak termed an *amorphous halo*. Note page 578 of Nerurkar et al. The mere difference in a physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of the instant amorphous form *vis-à-vis* the prior art amorphous forms.

Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9 and 39-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No support can be found for the newly recited chiral purities added to the claim. Only one working example in the specification recites a chiral purity, *i.e.*, example 1 recites 99.90% for esomeprasole magnesium. This recited chiral purity does not support the range of newly added chiral purities or the chiral purities for all the other instant salts.

Claims 9, 10, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and enablement requirements. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Again, the specification lacks description as to whether the amorphous form is thermodynamically stable as to provide utility at room temperature for these forms in the compositions. Page 6 of the specification recites conventional pharmaceutical excipents. In the instant specification, no example can be found as how the values of chiral purities of the amorphous forms are arrived in any solid or liquid compositions or what specific carriers are needed to stabilize the instant amorphous forms in the pharmaceutical compositions.

The pharmaceutical formulation field is well aware that amorphous forms when formulated into compositions may undergo transformation thus, the particular form may not be the same form after processing, compressing, etc. Note page 179 of Caira or Xu abstract (CA 140:20080, article now supplied) or Chopra et al on page 40).

The specification lacks description and enablement as to whether the amorphous form is thermodynamically stable as to provide utility at room temperature for these forms in the pharmaceutical compositions. The preponderance of evidence in the state-of-the-art indicates that the pharmaceutical formulation field is well aware that amorphous forms when formulated into compositions may undergo transformation thus, the particular form may not be the same form after processing, etc. Hence, pharmaceutical compositions containing any particular amorphous form cannot be described and enabled with specificity and particularity. For example, page 10 of the Doelker translation, states that the amorphous forms, not thermodynamically stable, in particular have a high solubility, subject to increasing the dissolution rate and the bioavailability. Further, Doelker states that amorphous novobiocince acid is transformed into crystalline form, non-resorable, in six months at ambient temperature, a phenomenon that it is possible to combat by adding methyl cellulose. The specification is silent to any specific carriers that may be employed to combat any conversion of the instant amorphous form.

Chemical & Engineering News disclose that formulation of drugs or pharmaceuticals in its metastable forms, for example, on polymorph, is highly unpredictable. The metastable forms will disappear and change into the most thermodynamically stable form. Note page 165 of Caira where it is specifically stated that polymorphs are known to "vanish" and attempts to regenerate the original polymorph are frequently met with failure. Muzaffar et al., p. 60 states "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form." And p. 63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism. Also, note page 179 of Caira.

The specification has not described how all the crystalline forms in the compositions being claimed will be maintained and prevented from converting to other forms .

The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. Applicants are referred to In re Fouche, 169 USPQ 429 CCPA 1971, MPEP 716.02(b).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention

The nature of the invention is the preparation of amorphous forms of esomperazole salts and pharmaceutical compositions.

State of the Prior Art

Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. (See Chemical Engineering News, page 32). Threifall et al on page 2452 recites that amorphous forms are usually characeterized inadequately, if at all, and it is not always possible even to ascertain if the reported lack of crystallinity is derived from visual examination, polarized light microscopy or X-ray examination. Nerurkar et al. on page 579 states that there is actually no

sharp distinction between the crystalline and amorphous states. No method exists to predict the polymorphs of a solid compound with any significant certainty. In drug design, it is best to work with the most stable polymorph, because it will not convert any further, however, the most stable polymorph usually is the least soluble. To improve bioavailability, drug companies sometimes trade off polymorph stability with solubility, choosing to work instead with the less stable forms first, also known as the metastable forms. Polymorphs can convert from one form to another during the manufacturing process of a pharmaceutical drug. See Chemical Engineering News, page 33. This is why it is important to monitor the polymorph during manufacture of the drug to see if it persists during manufacture.

The amount of direction or guidance and the presence or absence of working examples

The specification on page 2, paragraph 8, on lines 30-31, recites that a salt of esomeprazole in the amorphous form rather than the compositions being claimed may have an X-ray diffraction pattern of a plain halo. Based on the unpredictability in the art, the applicant is not entitled to the alleged X-ray diffraction pattern claimed for the compositions.

The breadth of the claims

The breadth of the claim are drawn to the specific amorphous forms and in addition to the compositions.

The quantity of experimentation needed

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to the compositions being claimed and verifying that they have the specific X-ray diffraction patterns being claimed which are not disclosed in the specification.

In terms of the 8 Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of unpredictability in the art of the invention, and the poor amount of direction provided by applicants. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 6, 7, 9 and 39-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Again, claims 1, 2, 4, 6, 7, 9 and 39-41 contain the generic name esomeprazole. Where a generic name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the generic name cannot be used properly to identify any particular material or product. In the present case, the generic name is used to identify/describe a chemical compound having a specific chemical structure and, accordingly, the identification/description is indefinite.

The claims measure the invention. United Carbon Co. V. Binney & Smith Co., 55 USPQ 381 at 384, col. 1, end of 1st paragraph, Supreme Court of the United States (1942).

The U.S. Court of Claims held to this standard in Lockheed Aircraft Corp. v. United States, 193 USPQ 449. The claims measure invention and resolution of invention must be based on what is claimed.

The C.C.P.A. in 1978 held that an invention is the subject matter defined by the claims submitted by the applicant. We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim. In re Priest, 199 USPQ 11, at 15.

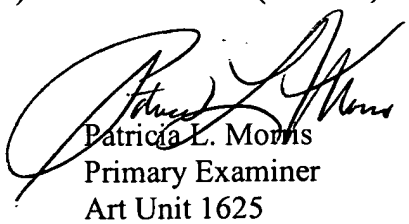
Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688. The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Patricia L. Morris
Primary Examiner
Art Unit 1625

plm
February 5, 2008